Diagnosis and management of motor neurone disease

Christopher J McDermott, Pamela J Shaw

Sheffield Care and Research Centre for Motor Neurone Disorders/Academic Neurology Unit, Section of Neuroscience, University of Sheffield, Sheffield S10 2RX

Correspondence to: C J McDermott
Christopher.Mcdermott@sth.nhs.uk

BMJ 2008;336:658-62
doi:10.1136/bmj.39493.511759.BE

Motor neurone disease is a devastating illness which leads to progressive paralysis and eventual death. We will discuss the presentation of motor neurone disease in primary care and update non-specialists on progress with regards to life prolonging interventions, better control of disease symptoms, and an increased understanding of disease mechanisms. Motor neurone disease is rare but patients often are aware of it, so this review should help non-specialists reassure patients in whom it is unlikely to be the diagnosis.

Sources and selection criteria

The review is based on our experience in running the Sheffield Care and Research Centre for Motor Neurone Disorders and an up to date review of the current literature relating to motor neurone disease. Searches used PubMed and the Cochrane Library databases.

How common is motor neurone disease?

Motor neurone disease is relatively uncommon with an annual incidence of 2 in 100 000 and prevalence of 5-7 per 100 000.[1-3] General practitioners can expect to see one or two cases during their career.

How does motor neurone disease present?

Motor neurone disease is largely a sporadic disease of middle and elderly life presenting in the sixth and seventh decades, although the disease can present in much younger patients. A younger presentation is more often seen in familial motor neurone disease, which accounts for approximately 5% of cases. The classic form of the disease is also referred to as amyotrophic lateral sclerosis and presents with a mixture of upper and lower motor neurone features, such as wasted fasciculating biceps with a brisk or easily obtained biceps deep tendon reflex. The rarer variants of the disease can have a pure upper motor neurone presentation, primary lateral sclerosis, or a pure lower motor neurone presentation, progressive muscular atrophy.

Classic motor neurone disease tends to be focal in onset, with a particular group of muscles affected first. Of the three recognised patterns—limb, bulbar, and respiratory onset—limb onset is by far the commonest (box 1). In the upper limbs early symptoms are most commonly due to asymmetrical distal weakness, causing patients to drop objects or have difficulty manipulating objects with one hand, such as turning keys, writing, and opening bottles. Wasting of the intrinsic small muscles of the hand is common, particularly flattening of the thenar eminence and the first dorsal interosseous muscle, and often patients or relatives will have noticed this (fig 1 top). In the lower limbs early symptoms include foot drop, a sensation of heaviness of one or both legs, or a tendency to trip. Patients may also notice difficulty in rising from low chairs and climbing stairs or excessive fatigue when walking. On examination muscle wasting is often seen in the tibialis anterior (fig 1 middle).

Bulbar onset motor neurone disease occurs in about 20% of those affected. The first sign is usually slurring of the speech, caused by impaired tongue movement, which may be accompanied by obvious wasting and fasciculation of the tongue (fig 1 bottom). Dysphagia tends to occur later, when speech difficulties have become significant. Bulbar symptoms in motor neurone disease, as with other causes of pseudobulbar palsy, are often associated with emotional lability, manifesting as inappropriate laughing or crying.

The least common pattern of onset is when the respiratory muscles are affected first. Patients can

ADDITIONAL EDUCATIONAL RESOURCES

Motor Neurone Disease Association (www.mndassociation.org)—a comprehensive resource for patients, carers, and UK healthcare professionals on all aspects of motor neurone disease

World Federation of Neurology (www.wfnals.org)—details of amyotrophic lateral sclerosis clinics throughout the world and information on ongoing trials

Amyotrophic Lateral Sclerosis Association (www.alsa.org/)—comprehensive resource for patients, carers, and US healthcare professionals on all aspects of motor neurone disease

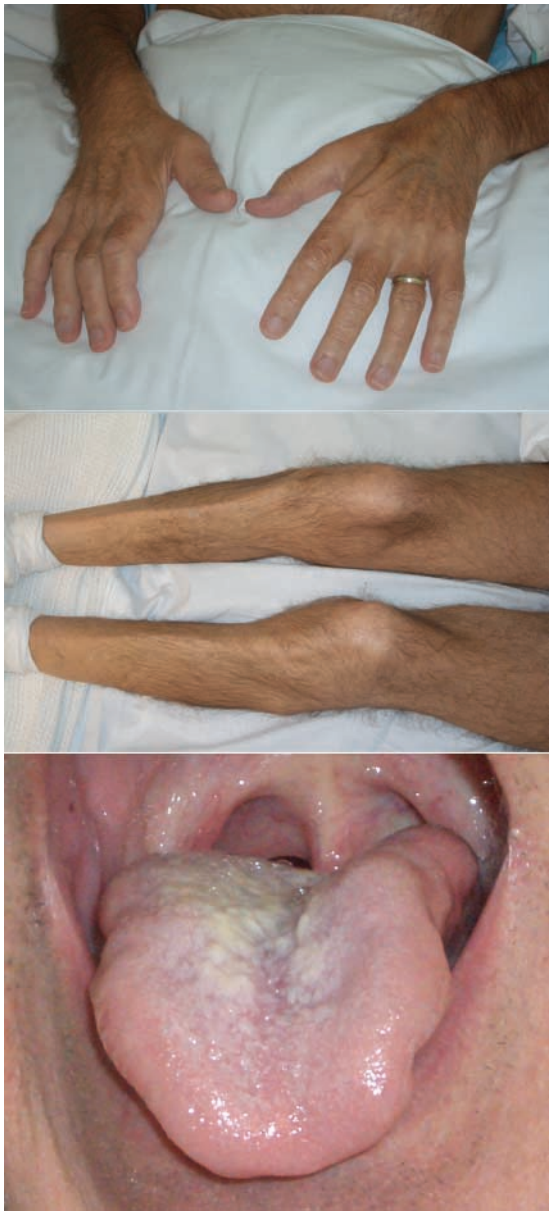

Fig 1 | Lower motor neurone loss leads to muscle wasting, particularly of first dorsal interossei (top), tibialis anterior (middle), and tongue (bottom)

present with dyspnoea and orthopnoea or more subtly with the clinical features resulting from hypoventilation overnight, including frequent waking, unrefreshing sleep, hypersomnolence, and early morning headaches.

How is motor neurone disease diagnosed?

A diagnosis of motor neurone disease relies on interpretation of the clinical symptoms and signs and use of investigations to exclude other causes. A person who presents with a painless, progressive loss of function in a weak, wasted limb or with one of the presentations described above would benefit from a neurological opinion. The lack of a definitive test can cause problems, particularly if patients are seen very early after onset of symptoms, when the signs may be limited. In these cases waiting and observation of the condition over weeks and months are needed. As with other disorders with such a grave prognosis, alternative cause for the patient's symptoms and signs must be excluded. Several conditions can mimic motor neurone disease and may be treatable, and it is important to consider these (box 2).

Giving the diagnosis—a personal view

Giving a diagnosis of motor neurone disease to a patient and their family, as with breaking any bad news, is a difficult task. Our approach is based on the well established good practice principles of breaking bad news.[4] We aim to impart information about the implications of the diagnosis honestly, but without destroying hope and with a positive emphasis on what can be done to help. Box 3 answers several common questions that patients and carers often ask in this consultation.

What life prolonging interventions are available?

Riluzole

Riluzole is the only drug identified to have a beneficial effect on survival, following a double blind, randomised placebo controlled trial in patients with the common amyotrophic lateral sclerosis variant of motor neurone disease.[5] The effect is modest, with a prolongation of life of approximately 3-4 months on average. It is generally well tolerated and it is now standard practice in the UK to commence riluzole therapy in all amyotrophic lateral sclerosis patients following diagnosis. These conclusions were confirmed by a Cochrane review examining evidence from four randomised clinical trials involving 1477 patients and are supported by NICE guidelines in the UK.[6]

Respiratory care

The greatest advance in recent years in treating motor neurone disease has been the discovery of the beneficial effects of non-invasive ventilation, in which the patient uses a mask ventilator system (usually bilateral positive airway pressure) overnight during sleep. The machines are small and portable, and various face masks are available (fig 2). On the whole patients quickly become accustomed to wearing the masks overnight. In later stages some patients may use non-invasive ventilation during the day, using a small nasal mask.

A randomised controlled trial found a median survival benefit of about seven months in patients with good bulbar function using non-invasive

Box 1 Diagnostic pointers in primary care for limb onset motor neurone disease

- Asymmetrical distal weakness often occurs
- Brisk reflexes in a wasted limb
- Absence of major sensory symptoms and pain
- Relentless progression of symptoms and signs during follow-up period

Box 2 Diseases mimicking motor neurone disease

Benign cramp fasciculation syndrome—Fasciculation or cramps, often affecting large muscles, particularly calves. Fasciculation is more common after exercise or periods of sleep deprivation. There is no wasting or weakness on examination and no progression after an interval

Cervical radiculomyelopathy—Multilevel degenerative disease of the cervical spine can present with a mixture of lower (wasting and weakness) and upper (brisk reflexes and spasticity) motor neurone signs. Pain (localised to neck or radicular) and sensory disturbance are clues to the possibility of this diagnosis. The lack of bulbar territory symptoms and signs and the lack of upper motor neurone signs above the lower motor neurone signs would also increase suspicion of this diagnosis. Magnetic resonance imaging of the cervical spine will help confirm this diagnosis

Dual pathologies—A cervical myelopathy and a coexistent peripheral neuropathy can present as a mixed upper-lower motor neurone picture. Sensory signs and symptoms and lack of bulbar symptoms are likely to help identify this, as will the neurophysiological assessment and imaging.

Multifocal motor neuropathy with conduction block—Often presents in young or middle agedmen as unilateral distal upper limb weakness with little evidence of wasting initially. This is an important rare diagnosis to consider in differential diagnosis of motor neurone disease. In the correct clinical context, it can be diagnosed or excluded only by careful neurophysiological evaluation looking for conduction block. It is treatable and has a markedly different prognosis than that for motor neurone disease

Inclusion body myositis—This inflammatory myopathy can present with distal weakness without sensory symptoms. Clinically long finger flexors are often affected preferentially, which would be unusual in MND. An EMG and sometimes a muscle biopsy are needed to confirm the diagnosis. Although resistant to treatment, inclusion body myositis has a more benign prognosis than MND

ventilation.[7] The extended survival was associated with an improvement in multiple quality of life measures—an important observation as one does not wish to extend life merely to prolong suffering. This effect on survival is much greater than that currently provided by neuroprotective treatments such as riluzole.

Antioxidants

Given the evidence that oxidative damage by free radicals occurs as part of the pathogenic process in motor neurone disease, there has been great interest in trialling antioxidant treatments.[8] The results have been disappointing, and a recent Cochrane review concluded that the use of antioxidants was not supported by currently available clinical trial data.[9]

What supportive interventions are available?

There is now a wealth of experience in managing the multiple symptoms experienced by patients with motor neurone disease (table). Although most of these interventions have not been the subject of robust clinical trials, they are standard clinical practice in specialist centres throughout the world.[10]

Nutrition and feeding

Most patients will eventually have difficulty swallowing. Early in the disease dysphagia can be managed by an experienced speech therapist and dietitian. Avoiding problem foods, position when eating (upright, no distractions, chin tuck), and changing to thickened fluids can be helpful.

Malnutrition may occur as the disease progresses because loss of limb strength and dexterity, or dysphagia, make feeding difficult. Malnutrition and weight loss are associated with a shortened survival.[11,12] Current practice is to offer the option of enteral feeding to patients either through percutaneous endoscopic gastrostomy, percutaneous radiological insertion of gastrostomy, or nasogastric tube when more than 10% of their premorbid weight has been lost or body mass index falls to below 18.5. We also consider enteral feeding if meals are becoming an ordeal because they last a long time or cause distressing coughing and choking. Radiological insertion of gastrostomy is the enteral feeding option of choice, as it has a higher success rate and is better tolerated, and as no or little sedation is required it can be considered in patients with compromised respiratory function.[13]

Multidisciplinary team

Multidisciplinary motor neurone disease clinics improve care, reduce the frequency and length of inpatient stays, and improve survival.[14] The team may include a neurologist, physiotherapist, occupational therapist, specialist nurse, social worker, dietitian,

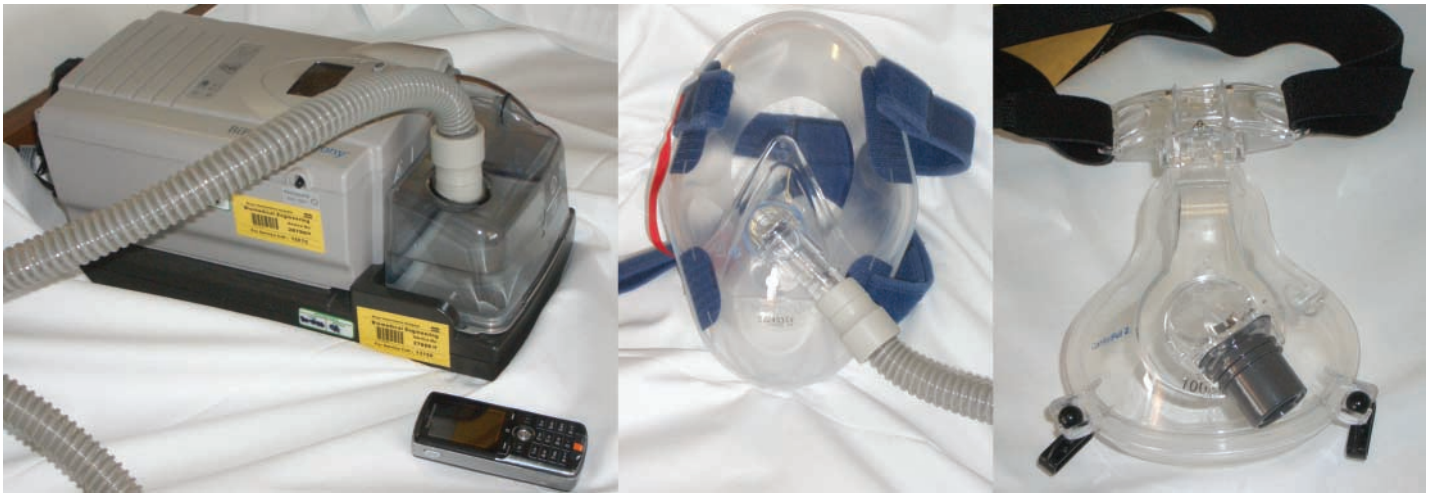

Fig 2 | Machine and masks for non-invasive ventilation

Managing symptoms in motor neurone disease[10]

Symptom	Drug	Comment
Difficulty swallowing saliva	Hyoscine patch*, atropine, amytriptyline, glycopyrrolate, botulinum toxin injection of salivary glands*, parotid irradiation*, portable suction device	
Thick saliva or bronchial secretions	Mucolytics such as carbocisteine (250-750 mg three times a day), nebulised saline with or without β receptor antagonosis or anticholinergics	Ensure patient is not dehydrated, avoid mouth breathing. Pineapple, apple or lemon juice can help
Cramp	Quinine sulphate, physiotherapy, magnesium, carbamazipine, verapamil	
Spasticity or jaw spasm	Physiotherapy†, baclofen, dantrolene, tizanidine, clonazepam	
Emotional lability, depression	Amytriptyline, selective serotonin reuptake inhibitors such as citalopram	
Urinary frequency	Amytriptyline, oxybutinin, detrusitol	
Constipation	Movicol, lactulose, docusate, senna, co-danthromer	Ensure patient is not dehydrated; assess fibre intake
Choking (laryngospasm) or respiratory distress	Lorazepam (0.5-2.5 mg sublingually) for short spells	Breathing space kit is available by request from the Motor Neurone Disease Association
	Oral morphine 2.5 mg four to six times a day for longer spells	
	Subcutaneous morphine 0.5 mg/hr and titrate for severe and prolonged dyspnoea	

*Level of evidence: class IV.
†Level of evidence: class IIB.

speech and language therapist, respiratory nurse, and respiratory and palliative care doctors. In our model the neurologist has a coordinating role, ensuring that the often rapidly changing needs of the patient are being anticipated and met.

End of life care

Despite a focus on helping people to live with motor neurone disease after diagnosis, inevitably the disease will progress, and the provision of effective end of life care is very important. Patients and carers vary in the wish to discuss the terminal phases of the disease, and our practice is to create the opportunity for staged discussion of this topic guided by the wishes and questions of the patient and their family. Hospice care is an option for patients entering the later stages of disease, and this can be introduced gradually as a form of respite for caregivers. If requested, information on advanced directives and naming of healthcare advocates should be available, along with help in implementing the patient's wishes. If they occur, these can be managed to allow a peaceful death in the patient's home or other environment of their choosing. Any signs of respiratory distress can be treated with opiates, which can be gradually titrated according to the patient's symptoms, with little risk of shortening

Box 3 Common questions asked by patients on receiving a diagnosis of motor neurone disease

Can motor neurone disease run in my family? In most cases it does not run in the family. Rare familial forms do occur (approximately 5% of cases) but more often than not this is already known about in the family. Therefore genetic testing is not routinely performed in isolated cases

Have I developed motor neurone disease because of something I have done? The cause of motor neurone disease is unknown. There is no firm evidence to suggest that any particular lifestyle or behaviour increases the risk of developing the disease

Will my mind or memory be affected by the motor neurone disease? Most patients and their families do not notice any change in their cognitive function. The injury to the nervous system selectively affects the motor neurone cells, sparing other types of cells

How long will I live? The range of survival is broad, with some patients succumbing to rapidly progressive disease within six months and others living for 10 years or more. Most patients fall somewhere between these extremes. On average people live two to three years after diagnosis[3]

Box 4 Recent promising advances in motor neurone disease

TDP-43

TAR DNA binding protein 43 has recently been identified as the main component of the ubiquitinated protein inclusions which are found within surviving motor neurons and are the pathological hallmark of sporadic motor neurone disease.[19] The finding of the same inclusions in frontotemporal dementia, dementia related to amyotrophic lateral sclerosis, and progressive muscular atrophy suggest these are all part of a disease spectrum

Role of microglial and astrocytes

Recent studies have shown that cells other than motor neurones have an important role in the pathogenesis of motor neurone disease.[20] Microglia, the main immune cells of the central nervous system, are activated early on in the disease, even before clinical signs of motor neurone injury are evident. Selectively suppressing the expression of mutant SOD1 in microglial cells in a transgenic mouse model of motor neurone disease significantly improved survival.[21] Astrocytes are the most abundant non-neuronal cell within the nervous system. Their functions include structural and metabolic support of neurones, as well as reuptake of neurotransmitters such as glutamate. Astrocytes expressing mutant SOD1 release a soluble factor that is toxic to healthy spinal motor neurones.[22] These major developments open new areas for investigation into the pathogenesis of the disease and new therapeutic targets to ameliorate disease progression

Gene studies

Genome-wide analysis and gene expression profiling do not make assumptions about the nature or location of possible causative genes and allow new pathways that may be implicated in motor neurone disease pathogenesis to be identified[17 23-25]

SUMMARY POINTS

Motor neurone disease is relatively uncommon, with an annual incidence of 2 in 100 000; general practitioners may expect to see one or two cases during their career

It usually develops in the sixth and seventh decades but can present much earlier; younger presentation is more often seen in familial motor neurone disease, which accounts for about 5% of cases

Riluzole is the only drug that has a beneficial effect on survival, prolonging life for three or four months

Non-invasive ventilation has been shown to prolong life and improve quality of life

life.[15] Sublingual lorazepam (0.5-2.5 mg) quickly relieves paroxysmal choking episodes, which are often due to laryngospasm. For more prolonged dyspnoea, start oral morphine at 2.5 mg 4-6 times a day and titrate up as required. For severe and prolonged dyspnoea, use subcutaneous morphine starting at 0.5 mg/h and titrating as needed.[10] More than 90% of patients die in their sleep, as a result of increasing hypercapnia, and choking to death is not seen in clinical practice.[15]

Future treatments

The scientific understanding of disease pathogenesis in motor neurone disease has had several exciting developments. Although these discoveries do not translate into immediate benefit for patients with the disease, they open up new avenues of investigation for potential future treatments (box 4). As dysregulation of several biological processes contributes to motor neurone injury,[16] a cocktail of neuroprotective agents targeting different pathways may offer the best hope of exerting a major impact on disease progression. The role of embryonic stem cells is unclear. Neuronal stem cells injected into the spinal cord are unlikely to ever be able to extend long axons out into the periphery to form appropriately effective connections with muscle, but recent evidence suggests that stem cells may exert beneficial effects on diseased motor neurones through alternative mechanisms.[17 18]

Conclusion

Motor neurone disease remains a devastating illness, and although no breakthrough has been made in terms of a cure, we can offer patients various interventions to enable longer survival with maintenance of independence and a good quality of life.

Contributors: The article was researched and written jointly. Both authors are guarantors.
Competing interests: None declared.
Provenance and peer review: Commissioned; externally peer reviewed.

1 Scottish Motor Neuron Disease Register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989. *J Neurol Neurosurg Psychiatry* 1992;55:536-41.
2 O'Toole O, Traynor BJ, Brennan P, Sheehan C, Frost E, Corr B, et al. Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. *J Neurol Neurosurg Psychiatry* 2008;79:30-2.
3 Worms PM. The epidemiology of motor neuron diseases: a review of recent studies. *J Neurol Sci* 2001;191:3-9.
4 Borasio GD, Sloan R, Pongratz DE. Breaking the news in amyotrophic lateral sclerosis. *J Neurol Sci* 1998;160(suppl 1):S127-33.
5 Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet* 1996;347:1425-31.
6 Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2007(1):CD001447.
7 Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurology* 2006;5:140-7.
8 Barber SC, Mead RJ, Shaw PJ. Oxidative stress in ALS: A mechanism of neurodegeneration and a therapeutic target. *Biochim Biophys Acta* 2006;1762:1051-67.
9 Orrell RW, Lane RJ, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2007(1):CD002829.
10 Andersen PM, Borasio GD, Dengler R, Hardiman O, Kollewe K, Leigh PN, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. *Eur J Neurol* 2005;12:921-38.
11 Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. *Neurology* 1999;53:1059-63.
12 Kasarskis EJ, Berryman S, Vanderleest JG, Schneider AR, McClain CJ. Nutritional status of patients with amyotrophic lateral sclerosis: relation to the proximity of death. *Am J Clin Nutr* 1996;63:130-7.
13 Thornton FJ, Fotheringham T, Alexander M, Hardiman O, McGrath FP, Lee MJ. Amyotrophic lateral sclerosis: enteral nutrition provision—endoscopic or radiologic gastrostomy? *Radiology* 2002;224:713-7.
14 Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. *J Neurol Neurosurg Psychiatry* 2003;74:1258-61.
15 O'Brien T, Kelly M, Saunders C. Motor neurone disease: a hospice perspective. *BMJ* 1992;304:471-3.
16 Barber SC, Shaw PJ. Molecular mechanisms of motor neuron degeneration in amyotrophic lateral sclerosis. In: Eisen A, Shaw PJ, eds. *Motor neuron disorders*. Amsterdam: Elsevier, 2007:57-88. (Handbook of Clinical Neurology, 3rd ed.)
17 Ferraiuolo L, Heath PR, Holden H, Kasher P, Kirby J, Shaw PJ. Microarray analysis of the cellular pathways involved in the adaptation to and progression of motor neuron injury in the SOD1 G93A mouse model of familial ALS. *J Neurosci* 2007;27:9201-19.
18 Mazzini L, Mareschi K, Ferrero I, Vassallo E, Oliveri G, Nasuelli N, et al. Stem cell treatment in amyotrophic lateral sclerosis. *J Neurol Sci* 2008;265:78-83.
19 Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130-3.
20 Monk PN, Shaw PJ. ALS: life and death in a bad neighborhood. *Nat Med* 2006;12:885-7.
21 Boillee S, Yamanaka K, Lobsiger CS, Copeland NG, Jenkins NA, Kassiotis G, et al. Onset and progression in inherited ALS determined by motor neurons and microglia. *Science* 2006;312:1389-92.
22 Nagai M, Re DB, Nagata T, Chalazonitis A, Jessell TM, Wichterle H, et al. Astrocytes expressing ALS-linked mutated SOD1 release factors selectively toxic to motor neurons. *Nat Neurosci* 2007;10:615-22.
23 Dunckley T, Huentelman MJ, Craig DW, Pearson JV, Szelinger S, Joshipura K, et al. Whole-genome analysis of sporadic amyotrophic lateral sclerosis. *N Engl J Med* 2007;357:775-88.
24 Schymick JC, Scholz SW, Fung HC, Britton A, Arepalli S, Gibbs JR, et al. Genome-wide genotyping in amyotrophic lateral sclerosis and neurologically normal controls: first stage analysis and public release of data. *Lancet Neurol* 2007;6:322-8.
25 Jiang YM, Yamamoto M, Kobayashi Y, Yoshihara T, Liang Y, Terao S, et al. Gene expression profile of spinal motor neurons in sporadic amyotrophic lateral sclerosis. *Ann Neurol* 2005;57:236-51.

Endpiece
Source of creativity

The simple act of focusing on things that are normally taken for granted is a powerful source of creativity.
Edward de Bono

Submitted by Alistair Tindall, *specialist registrar, London*